# EXHIBIT 30

related hepatitis. Am Rev Respir Dis 1978; 117:991.

4. Skolnick JL, Stolar BS, Katz DB, Anderson WH. Rifampin, oral contraceptives, and pregnancy. JAMA 1976; 236:1382.

5. Rizack MA, Hillman C. The medical letter: handbook of adverse drug interactions. New York: The Medical Letter, 1985.

6. Snider DE, Graczyk J, Bek E, Rogowski J. Supervised six-months treatment of newly diagnosed pulmonary tuberculosis using isoniazid, rifampin and pyrazinamide with and without streptomicin. Am Rev Respir Dis 1984; 130:1091.

7. Snider DE, Cohn DL, Davidson PT, Hershfield ES, Smith MH, Sutton FD. Standard therapy for tuberculosis. Chest 1985; 87(2):1175.

8. British Thoracic and Tuberculosis Association, Short Course Chemotherapy for Tuberculosis. Lancet 1976; 2:1102.

9. Kopanoff DE. A continuing survey of tuberculosis primary drug resistance in the United States: March 1975 to November 1977. Am Rev Respir Dis 1978; 118:835.

10. Snider DE, Long MW, Cross FS, Farer LS. Six-months isoniazid-rifampin therapy for pulmonary tuberculosis. Am Rev Respir Dis 1984; 129:573.

11. Stead WW, Dutt AK. Chemotherapy for tuberculosis today. Am Rev Respir Dis 1982; 125:94.

12. Zierski M. Prospects of retreatment of chronic resistant pulmonary tuberculosis patients: a critical review. Lung 1977; 154:91.

13. Abernathy AS, Dutt AK, Stead WW, Moers DJ. Short-course chemotherapy for tuberculosis in children. Pediatrics 1983; 72:801.

14. Dormer BA, Harrison I, Swart JA, *et al.* Prophylactic isoniazid protection of infants in a tuberculosis hospital. Lancet 1959; 2:902.

15. Dutt AK, Moers D, Stead WW. Short-course chemotherapy for extrapulmonary tuberculosis. Ann Intern Med 1986; 104:7.

16. Snider DE, Layde RM, Johnson MW, Lyle MA. Treatment of tuberculosis during pregnancy. Am Rev Respir Dis 1980; 122:65.

17. Snider DE, Powell KE. Should women taking antituberculosis drugs breast-feed? Arch Intern Med 1984; 144:589.

18. Andrew OT, Schoenfeld PY, Hopewell PC, Humphrey MH. Tuberculosis in patients with end-stage renal disease. Am J Med 1980; 68:59.

19. Cross FS, Long MW, Banner AS, Snider DE. Rifampin-isoniazid therapy of alcoholic and nonalcoholic tuberculosis patients in a U.S. Public Health Service cooperative therapy trial. Am Rev Respir Dis 1980; 122:349.

20. Komaroff A. The practitioner and the compliant patient. Am J Public Health 1976; 66:833.

21. Farer LS. Chemoprophylaxis. Am Rev Respir Dis 1982; 125:3 (Part 2) 102.

22. Mitchell JR, Zimmerman HJ, Ishak KG. *et al.* Isoniazid liver injury: clinical spectrum, pathology and probable pathogenesis. Ann Intern Med 1976; 84:181.

23. IUAT. Efficacy of various durations of isoniazid preventive therapy for tuberculosis. Bull WHO 1982; 60:555.

24. Snider DE, Caras GJ, Koplan JP. Preventive therapy with isoniazid. JAMA 1986; 255:1579.

25. Koplan JP, Farer LS. Choice of preventive treatment for isoniazid resistant tuberculous infection. JAMA 1980; 244:2736.

26. Luelmo F. BCG vaccination. Am Rev Respir Dis 1982; 125:3 (Part 2) 70.

27. WHO. Vaccination against tuberculosis. WHO/Technical Report Series 651, 1980.

# THE DIAGNOSIS OF NONMALIGNANT DISEASES RELATED TO ASBESTOS

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, MARCH 1986.

## Objective

The health effects of asbestos have become a cause of serious concern in recent years. It has been estimated that from 1940 to 1979, in the United States alone, 27,500,000 individuals were exposed to this mineral at work. Recognition of the diseases caused by asbestos exposure has led manufacturers to reduce exposure in a variety of ways, such as by using alternative materials and by instituting improved work practices. It has also led to widespread public concern over the presence of asbestos in the environment, and fear on the part of persons with minimal exposure. This and projections of future asbestos related illness have posed important public policy questions—whether to remove all asbestos in public buildings and what to do about the enormous estimated legal liability. In this context, physicians are commonly asked for advice. Furthermore, they are also consulted regarding the diagnosis of an asbestos-related respiratory condition in an exposed individual. While abundant literature exists on the health effects of asbestos, there is much that is conflicting. Accordingly, this report has been prepared by a group of experts to present an authoritative consensus view of the current state of knowledge while pointing out areas where additional information is necessary. An attempt is made to summarize our present knowledge on the diagnosis of nonmalignant asbestos-related pulmonary disease and provide the sources on which the opinion is based.

Reprints may be requested from your state or local Lung Association.

## Asbestos—the Mineral

The generic term "asbestos" is used to describe a group of minerals which, when crushed, break into fibers rather than dust. They are hydrated fibrous silicates which have great tensile strength, heat resistance, acid resistance, and some varieties are also flexible. This weavable rock has numerous important uses in an industrial society, and world production and use climbed steadily since its commercial introduction in the late 19th century. Geology, mineralogy, and uses have been well described elsewhere (1, 2). World production of asbestos has dropped markedly since the mid 1970's. The cumulative production of asbestos, however, continues to increase. There has been a good deal of debate about the mineralogic definitions of asbestos and asbestiform fibers. The most complete recent discussion on trends in asbestos production and now widely accepted mineralogic definitions are found in the NAS Report on asbestiform fibers (3).

## Asbestos in Lung Tissue

Inhaled asbestos that is retained in the lung can become coated with a proteinaceous iron staining material. The resulting asbestos or ferruginous body is a most characteristic index of asbestos exposure. It is usually recognized by its beaded-necklace or drumstick appearance. The longer fibers are more likely to become coated (2–22). The core of asbestos, i.e., bodies found in human lungs, is more likely to be an amphibole fiber than to be chrysotile, perhaps due to the greater ability of the former to survive in lung tissue, while chrysotile tends to disappear over time. The majority of the lung burden of asbestos, however, is uncoated and consists of short fibers, i.e., less than 5 microns (2–21). These are poorly visible or invisible on light microscopy but have been demonstrated by phase microscopy and electron microscopy. Asbestos bodies are commonly found in small numbers in lungs of city dwellers at routine autopsies in the absence of occupational exposure to asbestos and asbestos related illness. These are usually few in number and unassociated with pathologic abnormality in the parenchyma. This observation emphasizes the importance of developing standardized techniques to quantify the number and type of asbestos fibers in lung tissue (to be discussed below).

## Benign Pleural Abnormalities Associated with Asbestos

Asbestos causes pleural plaques, pleural thickening and pleural effusion. Pleural plaques are discrete, elevated, opaque, shiny, rounded lesions. They characteristically occur on the posterolateral aspect of the lower parietal pleura or diaphragm, but usually not on the visceral pleura, at the costophrenic angles, or at the apices. Thin plaques are smooth and grayish-white. Thicker ones are ivory-colored or gray and may have either a smooth surface or bosselated surface, or be coarsely nodular with the consistency of cartilage. Plaques are of two types, diffuse or nodular, and elevated. They can vary in size and shape. On inspection of gross specimens, calcification may be present but is not common. Microscopically, plaques are seen to be laminated collagenous connective tissue, acellular, with few inflammatory or fibrocytic nuclei; many are covered by a thin layer of regular and well-differentiated mesothelial cells. Capillaries are rare (23, 24). Elastic staining shows intact lamellae be-

neath the plaque in continuity with the surrounding normal parietal pleural connective tissue, suggesting that plaques are extrapleural and develop between the latter and its covering layer of mesothelial cells (23). On microscopic examination, calcium deposition is present in a large proportion of plaques, and occurs as deposits along the course of the collagen fibers, ceasing abruptly where the connective tissue changes into normal pleural tissue (23). Well-differentiated cuboidal mesothelial cells are present on the surface and the edges of the plaque (23); metaplastic changes are uncommon (24, 25).

Although coated asbestos fibers have not been reported in relation to pleural plaques in the extensive series of 172 sections examined by Meurman (23) using polarized light, the presence of many uncoated fibers may be noted when ashed tissue is studied (26, 27). Recent studies of the digestate of a small number of plaques has demonstrated the presence of submicroscopic fibers of both chrysotile and amosite fiber in these structures. It is of interest that these are more concentrated in the calcified zones than in the fibrous zones (28).

The usual effect of asbestos on the visceral pleura is a focal or diffuse thickening. This varies from a thin, milky white discoloration, detectable only on gross visualization to a thick peel encasing the lung and easily seen on chest roentgenogram. In contrast to plaques, which are frequently diagnosed roentgenologically in asymptomatic persons, pleural fibrosis may cause symptoms and impair pulmonary function.

Pleural effusion may be caused by inhalation of asbestos; this is an early manifestation and is usually an exudate. On rare occasions it may persist for months or years. It may recur on the same or the opposite side after several years of exposure. In unusual circumstances it may be bilateral. Macroscopically, the fluid may be blood stained with variable numbers of erythrocytes, macrophages, lymphocytes, and mesothelial cells (29).

## Pulmonary Asbestosis

### *Definition*

The term asbestosis should be reserved for the interstitial fibrosis of the pulmonary parenchyma in which asbestos bodies or fibers may be demonstrated. While pleural abnormalities are commonly associated with parenchymal disease, they should be separately classified as there are differences between pleural and parenchymal fibrosis in epidemiology, clinical features, and prognosis.

### *Pathologic Features*

In lungs with minimal or moderate fibrosis, the changes may be subtle and difficult to demonstrate. On examination of gross specimens, they appear as gray opaque areas devoid of air spaces in an otherwise brown lung. The microscopic changes in pulmonary asbestosis vary from small areas of basal fibrosis to a diffuse, fine fibrosis of both lungs. In general, the more extensive the process the smaller the volume of the lungs. The cut surface of the lung has a dark brown color with streaks of a fine, gray-colored fibrosis that generally appears to affect subpleural areas first and, frequently, in multiple and separate areas. This fibrosis may accentuate lobar and lobular septa and extends projections into the lung parenchyma. The parenchymal fibrosis, which has a linear and reticular appearance by X-ray, affects the lower lobes first, and extends upward with prolonged or heavy exposure (10, 30, 31). The fibrosis may take one of three forms. One is a diffuse fibrosis without air space enlargement; a second form is called honeycombing. This form may affect the lower lobes and subpleural regions (31). The third form is a combination of both diffuse fibrosis and honeycombing. This latter form is the one most frequently observed. The honeycombing is characterized by enlarged thick-walled air spaces ranging in size from 1 to 15 mm (32). The pleural surface adjacent to the fibrosis is invariably involved in the fibrotic process, either mildly with the appearance of a milky covering to the fibrosis, or with widespread fibrosis and symphysis (30, 31). The hilar lymph nodes are only slightly enlarged and soft unless other disease coexists. While emphysema has been reported in the past, it is unusual, and may have been incorrectly labelled as honeycombing (10, 33).

### *Microscopic Appearances*

There is little information on the early pathophysiology of asbestosis in humans. Current opinion is largely based on inferences from animal studies. Some evidence exists that release of lysosomal enzymes may result from the partial ingestion of the asbestos fibers and the incomplete fusions of the phagosome membrane, so allowing the release of enzymes into the medium from lysosomes which have fused with the phagosome. The cytotoxic activity of asbestos exhibited by the release of lysosomal enzymes may result from the fibers penetrating intracellular structures, such as the nucleus and lysosomes, by preventing the movement of organelles within the cytoplasm, or by disrupting the cytoplasmic organization provided by microfilaments and microtubules (34). In any case, the initial reaction to asbestos fiber introduced into the lung is the immediate exudation of neutrophils and macrophages into the alveolar spaces in the locus of asbestos. This exudate varies with the age of the lesion. In the initial stages the exudate may be predominantly neutrophilic. Macrophages are the most common cells in the infiltrate. The inflammatory infiltrate soon is associated with varying degrees of organization with fibrosis (35, 36). The process is believed to be concentrated initially in peribronchiolar regions (10, 30). The initial lesion after exposure by inhalation is in the region of the respiratory or terminal bronchioles. There is a macrophage exudate in the lumen associated with asbestos fibers and bodies. Metaplasia of the cuboidal epithelium to squamous type may occur. In the early stages, fibrosis may be minimal but, when present, is in the respiratory and terminal bronchiolar regions and in the alveoli arising from the most proximal alveolar ducts. Alternatively, there may be coboidalization of the epithelial cells. Characteristically, in early stages only an occasional pulmonary subunit is involved. More advanced cases show a diffuse fibrosis, involving the interstitium, frequently associated with areas of extensive fibrosis with obliteration of air spaces and condensation of the bronchovascular structures. Areas adjacent to the fibrosis may show accumulation of alveolar macrophages, some of which have ingested asbestos fibers or other fragments. Alveolar epithelial hyperplasia may also occur. When moderate or severe degrees of fibrosis are present, the small pulmonary arteries and arterioles are thickened and sclerotic (30). (The presence of uncoated asbestos fibers and asbestos bodies in the presence of interstitial fibrosis is mandatory for the pathologic diagnosis of asbestosis.)

Before a pathologic diagnosis of asbestosis can be made we must consider a number of problems, including the following:

1. There are numerous other causes of interstitial fibrosis.
2. The distribution of interstitial fibrosis in asbestosis may be irregular, and therefore, adequate sampling of the lung must be done. The lingula and the right middle lobe are particularly prone to nonspecific fibrosis and sampling must take this into consideration.
3. While advanced asbestosis characteristically shows numerous asbestos bodies, they may not always be found because many fibers are cleared from the lungs and some, particularly chrysotile, may undergo dissolution and fragmentation with time (32). Thus, in unusual cases it may be difficult to demonstrate fibers or asbestos bodies in the histologic preparation. When that is the case, 5 to 10 additional sections from the same block, and 5 to 10 additional new blocks from areas with fibrosis, should be prepared, stained, and surveyed for asbestos bodies. If they are not found, the diagnosis of asbestosis is unlikely.
4. Even in the absence of a history of asbestos exposure, the presence of several or more asbestos bodies in areas of extensive interstitial fibrosis is sufficient evidence for a morphologic diagnosis of asbestosis.
5. Not everyone who inhales an asbestos fiber, or even a few fibers, develops even microscopic asbestosis. Normal lung defense mechanisms remove fibers via several well-described mechanisms.

The Pneumoconiosis Committee of the American College of Pathologists and the National Institute for Occupational Safety and Health dealt with these considerations when formulating the following statement with which we concur:

> "The criteria that permit the pathologist to establish the diagnosis of asbestosis have evolved during a review of many cases of the disease. Presently, the minimal features that permit the

diagnosis are the demonstration of discrete foci of fibrosis in the walls of respiratory bronchioles associated with accumulations of asbestos bodies. These morphologic findings, although adequate to establish the diagnosis of asbestosis in an early evolutionary stage, have not been shown to result in functional and radiologic alterations. The demonstration of asbestos bodies in the absence of fibrosis is insufficient evidence to justify the diagnosis of asbestosis. Conversely, a definite diagnosis of asbestosis cannot be made by the pathologist in cases that show characteristic fibrosis in the absence of asbestos bodies or other evidence of fibers. Because asbestos bodies are unevenly distributed in tissue, an adequate number of samples should be examined thoroughly." (32)

They further state that although the demonstration of asbestos fibers by the electron microscopic study of tissue digestates provides evidence of exposure, ultrastructural technique alone cannot be used to establish definitively the etiologic role of asbestos in disease (32).

This Committee has published guidelines for methods of assessing lung fiber concentration and pathologic grading of asbestosis. The certainty of the cause and effect relationship of asbestos to the fibrotic process increases with increasing numbers of such particles and fibers visualized by light microscopy. Electron microscopy of digested lung preparation from documented cases of asbestosis shows very large numbers of uncoated fiber fragments (37).

Since asbestos bodies and fibers appear in lungs without evidence of asbestos-related disease, the question arises as to how many such bodies are necessary to infer a cause and effect relationship between asbestos particles and fibrosis. No precise answer exists, but efforts to quantify the numbers of asbestos particles in known cases indicate that it is high. In the cases of asbestosis studied by Whitwell, the lungs nearly always showed three million light visible fibers per gram; control lungs generally show less than 20,000 fibers per gram (38).

Electron microscopy is a more sensitive index of asbestos exposure than light microscopy. It will detect 10 to 100 times more fibers than seen by light microscopy. Fibers seen only by light or electron microscopy, in the absence of parenchymal fibrosis, indicates only that exposure to asbestos has occurred. Additional studies are required to define the number of fibers in the lungs of persons with a variety of occupational exposures, and with varying periods of exposure, as well as in nonoccupational populations.

Investigations have demonstrated that as many as a million fibers per gram of dry tissue of chrysotile may be present in the lungs from nonoccupational exposures in the general population. By contrast, lungs containing a million fibers of amosite or crocidolite per gram are considered to reflect substantial occupational exposure to asbestos dust (39). An electron microscopic field of necessity represents a small sample of the lung and analysis of multiple fields is required to reflect the true asbestos lung burden. In our opinion, additional studies on the numbers and types of asbestos fibers in the lungs of control and exposed persons must be performed to provide the informational bases for interpretation of quantitative data concerning asbestos fibers in the lung and their relation to the presence of asbestosis or other asbestos related diseases.

### *Exposure History*

Numerous studies have shown that asbestosis has a relatively close association with both the magnitude and the duration of exposure to inhaled asbestos; the more intense and longer the exposure, the greater the numbers of affected workers and the greater the severity of their illness. There is no evidence that casual or indirect exposure, such as occurs in the general population, causes asbestosis. The major problem facing the clinician is to assess whether an exposure has been sufficient to cause disease. Although dust levels have been measured in many industries for many years, they are not usually available to or easily interpreted by clinicians. Nevertheless, some general statements can be made. A careful sequential history of all exposures to all potentially harmful substances is obviously important. Particular attention should be paid to occupations in which direct contact with asbestos has occurred. Consultation with physicians trained in occupational medicine or with industrial hygienists may be helpful in unclear cases.

Evidence of asbestosis has been found many years after relatively brief but extremely heavy exposure. Such exposure often occurred in the asbestos textile industry over 50 years ago and has occurred more recently in workers who have not used respiratory protection while spraying dry asbestos on steel beams. Fortunately, such exposure is rare at this time. With levels of exposure common in the past few decades, the latent period between the state of the exposure and the discovery of the manifestations of asbestosis is likely to be a minimum of 15 years, and more often considerably longer. With exposures below the current recommended permissible exposure limit value, asbestosis is not likely to be found during the course of a working career. With proper engineering controls, work practice, and where necessary, personal respiratory protective devices, asbestosis should not occur.

### *Clinical Diagnosis*

In the usual clinical setting, the diagnosis of asbestosis has to be made in the absence of histologic examination of lung tissue. Open lung biopsy is rarely indicated in the assessment of workers for compensation purposes. The benefit of the doubt should be given whenever the clinical features and occupational exposure data are compatible with the diagnosis. In most instances, the clinician and epidemiologist must still rely on indirect methods of diagnosing asbestosis. These principles of diagnosis are based on observations from pathologically proven cases. When biopsy is done, careful attention must be paid to the sampling considerations mentioned above and the surgical technique employed (40). Assessment of lung dust burden in such biopsy material is desirable. Diagnosis of asbestosis does not mean that measurable impairment of lung function or physical disability is necessarily present.

### *Clinical Features*

In advanced stages, asbestosis is a restrictive lung disease associated with dyspnea, clubbing of the fingers, basilar crackles and widespread irregular opacifications on roentgenograms. The latter are usually more prominent at the lung bases. Pleural thickening and calcification may also be present as noted above. The vital capacity is usually reduced with preservation of the $FEV_1/FVC$ ratio and gas exchange impaired. Cor pulmonale may occur in advanced disease. When many or all of these features are present the diagnosis is made without difficulty. However, in the absence of the opportunity to examine lung tissue microscopically, the diagnosis is always inferential. The certainty increases with increasing numbers and severity of typical clinical abnormalities.

The chest roentgenogram appears to be the most valuable examination in diagnosing asbestosis. A diffuse irregular interstitial pattern coupled with evidence of pleural disease, e.g., plaques or extensive pleural thickening in a person with known exposure, presents little diagnostic difficulty. The difficulty with the use of the chest roentgenogram relates to the detection of lesser degrees of interstitial fibrosis. Efforts have been made to standardize the interpretation of roentgenograms in the pneumoconioses. The most widely accepted and extensively studied method for assessing the degree of roentgenologic involvement in the pneumoconioses was developed by the International Labour Office and is currently called the ILO-1980 Classification (41). This scheme evolved from studies of miners and focused initially on the detection of silicosis. The X-ray appearance of silicosis is characterized initially by small rounded opacifications. The classification was later broadened to describe abnormalities which occur in asbestosis and do not have a rounded appearance. These are fine, medium and coarse, small irregular opacifications, and they are called s, t, and u, respectively. The classification, originally developed for describing radiologic changes in epidemiologic studies, has also been used in the clinical context for case detection and/or diagnosis. In the latter instance, the information given in the chest radiograph is added to all other information about the individual in order to arrive at a diagnosis.

The number of these abnormalities in a given area of the chest film, whether rounded or irregular, is called their profusion. The profusion was initially graded as 0 for none, 1 for slight, 2 for moderate, and 3 for severe.

It became apparent, however, that even experienced readers had difficulty in grading opacifications into these categories in a reproducible fashion. However, if observers were asked to give two classifications, i.e., the one category they thought was most likely and another which they thought might also be considered, the observer reliability (i.e., in terms of reproducibility) was considerably improved. This method of giving the observer two options (the one he thought most likely and next most likely) was called the expanded classification. It formed a 12-point scale that has proven to be very useful epidemiologically.

It is likely that an individual who develops asbestosis moves more or less uniformly from the normal roentgenologic appearances (-/0, 0/0, 0/1) to the abnormal (1/2, 2/1, 2/2, etc.). The problem is that the interpretation of the lesser degrees of abnormality on this scale is subjective and that numerous causes of such roentgenologic shadowing other than asbestosis exist. In the presence of marked diffuse pleural thickening, it is difficult to diagnose or grade the severity of interstitial fibrosis. Accordingly, criteria other than roentgenographic ones have been sought.

### *Dyspnea*

Asbestosis has been described as a monosymptomatic disease, dyspnea being the major complaint of the affected individual (42). There is no doubt that shortness of breath is common and troublesome in individuals with clinically significant interstitial fibrosis. Dyspnea, however, is a nonspecific symptom, common in many other cardiopulmonary disorders, and it is particularly subject to emotional factors likely to be relevant in instances of suspected industrially-related disease. Accordingly, it is not adequate to use dyspnea as the only evidence on which to base a clinical diagnosis of asbestosis in an individual at risk.

### *Clubbing*

Clubbing of the fingers occurs more commonly in asbestos-exposed workers than in controls (43, 44, 45). The diagnostic usefulness of clubbing is limited, however, by two important considerations. There are many other causes of clubbing and clubbing, when present, is a late finding in pulmonary asbestosis (46). Since the majority of persons with significant asbestosis do not have clubbing, and asbestos workers with clubbing may have it for reasons other than pulmonary fibrosis, the diagnostic usefulness of clubbing is limited.

### *Basilar Crackles*

Crackles have been recognized as a feature of asbestosis for over 50 years and are believed by many to be an early finding (47, 48, 49). They have been described as characteristic in their sound ("fine," "cellophane," "velcro," "close to the ear") and in their bilateral, basilar distribution (50). They differ in quality and timing from the crackles of bronchitis which tend to be fewer in number and earlier in timing. Bronchitic crackling begins with the beginning of inspiration and usually discontinues prior to mid or late inspiration. Characteristically, the crackles of interstitial fibrosis are pan inspiratory or have an end inspiratory accentuation. They appear first at the bases in the mid-axillary lines and tend to spread toward the posterior bases. As the disease advances, the crackles become distributed at progressively high levels up from the bases (50). They are often difficult to distinguish from the crackles of congestive heart failure. Reported rates vary, but about half of the persons considered to have asbestosis on clinical grounds have crackles (47, 51, 52, 53); prevalences in exposed populations range from about 10–20%. Such prevalences depend on duration of exposure, the age of the population, and prevalence of other diseases causing fine crackles. Observer variability exists in chest auscultation, but this can be reduced by training and waveform analysis (54, 55, 56). In summary, under carefully controlled circumstances crackles can be useful in diagnosing interstitial fibrosis. However, they are not also specific for the interstitial fibrosis related to asbestos.

### *Pulmonary Function*

The characteristic features of pulmonary asbestosis are those of a restrictive lung disease, i.e., a reduction in lung volumes, with inspiratory capacity and vital capacity being primarily affected, functional residual capacity being less affected, and residual volume even less. These changes are consistent with a decrease in pulmonary compliance. Hypoxemia may be present at rest or develop with exercise. Diffusing capacity is also usually impaired, depending on the extent of the disease. By contrast, large airway function as reflected in the $FEV_1/FVC$ ratio is generally well preserved. Review of the prediction formulas for pulmonary function tests reveals there is no one set applicable to all laboratories and patient populations. Predicted normal values used in pulmonary function laboratories should be based on regression equations from studies whose testing equipment, methodologies and control populations most clearly resemble the patients under study. Numerous studies have shown that the effects of asbestos on lung function are dose related (57, 58, 59).

There is convincing evidence that an asbestos related pulmonary abnormality can occur in the absence of definite radiologic change. These pathologic changes of early asbestosis have been demonstrated in biopsy material from asbestos-exposed individuals with minimal or no radiologic abnormality (60). Likewise, exposure response relationships for certain pulmonary function abnormalities (including reduced lung compliance and impaired flow at low lung volumes) have been demonstrated in asbestos-exposed subjects without radiologic abnormalities or reduction in vital capacity (58), and their occurrence subsequently confirmed in large animal models with biopsy confirmation of the associated pathologic changes. The impairment associated with such abnormality is usually modest.

### *Diffusing Capacity*

Diffusing capacity or transfer factor has been the subject of numerous studies with somewhat conflicting results. In most studies of unexposed populations it is lower in asbestos exposed workers than in normal controls although not always at a statistically significant level (44, 45, 57, 62, 63). There is not always a clear relationship to dust exposure indices (58, 64). It has, however, been shown to correlate with the severity of the histologic lesion in interstitial fibrosis (64), and its reduction can precede roentgenologic abnormalities. At this time a reduction of the diffusing capacity in an asbestos worker, in the absence of other known causes for impaired gas exchange, would provide suggestive evidence for asbestosis, but further population studies are necessary to elucidate the precise role of this test.

### *Other Studies*

Various other measurements have been employed for monitoring persons exposed to asbestos. A reduction in roentgenologic lung volume appears promising since it is applicable to serial studies of patients, but it requires careful control of inspiration (66). This approach has not yet been taken in a large number of subjects exposed to asbestos.

Inspiratory capacity was shown to be suitable for surveillance of workers but is not likely to add much more than vital capacity (VC) as the two tests are highly correlated (59). This finding suggests that tests for small airways disease might in the future be applicable to early detection (67). In one study, neither closing volume nor closing capacity correlated with the duration of exposure or with the asbestos dust index (68). Gallium scanning, bronchoalveolar lavage, and transbronchial biopsy need further evaluation with respect to their usefulness in diagnosing asbestosis. CT scanning is of particular value in detecting and quantitating pleural disease and aiding in the differentiation of pleural from parenchymal disease. The value of CT scanning in the detection of interstitial fibrosis also needs to be further evaluated. Thus, at this time, criteria other than crackles, restrictive lung functional abnormality, reduced diffusing capacity of the lung ($D_L$), and roentgenogram consistent with interstitial fibrosis of 1/1 or more are either impractical, of unproven value, or are not likely to yield additional information because of their high correlation with one of these four.

In our opinion, combinations of these abnormalities are more reliable in terms of specificity, relation to duration of exposure, consistency, and predictive value; however, little work has assessed combinations of abnormalities.

## Combinations

Combinations of abnormal test results are not

modern technology. Environ Res 1969; 2: 166.

19. Wright GW. Asbestos and health in 1969. Am Rev Respir Dis 1969; 100: 467.

20. Harries PG. Asbestos dust concentrations in ship repairing: A practical approach to improving asbestos hygiene in naval dockyards. Ann Occup Hyg 1971; 14: 241.

21. Respiratory Diseases: Task Force Report on Problems, Research Approaches, Needs. The Lung Program, National Heart and Lung Institute, October 1972, U. S. Department of Health, Education and Welfare.

22. Lee GL, Smith DJ. Steelwork insulated with sprayed crocidolite asbestos: Controlling a potential hazard. Ann Occup Hyg 1974; 17: 49.

23. Meurman L. Asbestos bodies in pleural plaques in a Finnish series of autopsy cases. Acta Pathol Microbiol Scand 1966; (Supplement) 181: 8.

24. Mattson SB, Ringqvist T. Pleural plaques and exposure to asbestos. Scand J Respir Dis 1970; (Supplement) 75: 4.

25. Lewinsohn HC. Early malignant changes in pleural plaques due to asbestos exposure: A case report. Brit J Dis Chest 1974; 68:121.

26. Roberts GH: The pathology of parietal pleural plaques. J Clin Path 1971; 24:348.

27. Hourihane DO, Lessof L, Richardson PC. Hyaline and calcified pleural plaques as an index of exposure to asbestos: A study of radiological and pathological features of 100 cases with a consideration of epidemiology. Brit Med J 1966; 1:1069.

28. Le Bouffant: Biological effects of asbestos. Bogovski P, Gilson JC, Timbrell V, Wagner JC, eds. Proceedings of a working conference at IARC, Lyon, October 2-6, IARC Scientific Publications, No. 8, Lyon, 1973; 249.

29. Hillerdal G: Non-malignant asbestos pleural disease. Thorax 1981; (Sept) 36(9):669–675.

30. Hourihane DO, McCaughey WTE. Pathological aspects of asbestosis. Postgrad Med J 1966; 42:613.

31. Heard BE, Williams R. The pathology of asbestosis with reference to lung function. Thorax 1961; 16:264.

32. The Pathology of Asbestos-Associated Disease of the Lungs and Pleural Cavities: Diagnostic criteria and proposed grading schema. Craighead JE, Chairman, Report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health. Arch Pathol Lab Med 1982; 106:544.

33. Solomon A, Goldstein B, Webster I, Sluis-Cremer GK. Massive fibrosis in asbestosis. Environ Res 1971; 4:430.

34. Johnson NF, Davies R. An ultra structural study of the effects of asbestos fibers on cultured peritoneal macrophages. Brit J Exptl Pathology 1981; 62:559–70.

35. Gaensler EA, Kaplan AI. Asbestos pleural effusion. Ann Intern Med 1971; 74:178.

36. Gaensler EA, Carrington CB, Coutu RE, Tomasian A, Hoffman L, Smith AA. Pathological, physiological and radiological correlations in the pneumoconioses. Ann N Y Acad Sci 1972; 200:574.

37. Miller A, Langer AM, Tierstein AS, Selikoff IJ. "Non-specific" interstitial pulmonary fibrosis: Association with asbestos fibers detected by electron microscopy. N Engl J Med 1975; 292:91.

38. Whitwell F, Scott J, Grimshaw M. Relationships between occupations and asbestos fibre content of the lungs in patients with pleural mesothelioma, lung cancer and other diseases. Thorax 1977; 32:377–86.

39. Churg A. Fiber counting and analysis in the diagnosis of asbestos-related disease. Human Pathology 1982; (April 13) 4:382–92.

40. Gaensler EA, Carrington CB. Open biopsy for a chronic diffuse infiltrative lung disease: Clinical, roentgenographic and physiological correlations in 502 patients. Ann Thorac Surg 1980; 30:411–26.

41. International Labour Office. Guidelines for the Use of ILO International Classification of Radiographs of Pneumoconioses. Rev. Ed. 1980. Occupational Safety and Health Series. No. 22, International Labour Office, Geneva, 1980.

42. Selikoff IJ, Churg J, Hammond EC. The occurrence of asbestosis among insulation workers in the United States. Biological Effects of Asbestos. Ann N Y Acad Sci 1965; 132:139.

43. Kleinfeld M, Massite J, Kooyman O, et al. Effect of asbestos dust inhalation on lung function. Arch Environ Health 1966; 12:741.

44. Regan GM, Tagg B, Walford J, et al. The relative importance of clinical, radiological and pulmonary function variables in evaluating asbestosis and chronic obstructive airway disease in asbestos workers. Clin Sci 1971; 41:569.

45. Wallace WFM, Langlands JHM. Insulation workers in Belfast. Comparison of a random sample with a control population. Br J Ind Med 1971; 28:211.

46. El-Sewefy AZ, Awad S, Abdel-Salam MS. Chest symptomatology in an Egyptian cement-asbestos pipe factory (a field survey). J Egypt Med Assoc 1970; 53:84.

47. Epler GR, Gaensler EA, Carrington CB. Crackles (rales) in the interstitial pulmonary diseases. Chest 1978; 73:333–39.

48. Shirai F, Kudoh S, Shubuya A, Sada K, Mikami R. Crackles in asbestos workers: Auscultation and lung sound analysis. Br J Dis Chest 1981; 75:386–96.

49. Elmes PC. Health parameters other than mesothelioma. Proceedings of Asbestos Symposium, Johannesburg, South Africa, October 3-7, 1977. National Institute for Metalllurgy, Randburg 1978; 9–16.

50. Smither WJ. Secular changes in asbestosis in an asbestos factory. Biological Effects of Asbestosis. Ann N Y Acad Sci 1965; 132:166.

51. Rossiter CE, Berry G. The interaction of asbestos exposure and smoking on respiratory health. Bull Europ Physiopath Resp 1978; 14:197–204.

52. Huuskonen MS. Clinical features, mortality and survival of patients with asbestosis. Scand J Work Environ & Health 1978; 4:265–74.

53. Segarra F, Baselga MM, Lopes IP, Perez NJ. Asbestosis in a Barcelona fibrocement factory. Environ Research 1980; 23:292–300.

54. Workum P, Del Bono EA, Holford SK, Murphy RLH. Accuracy of a technician in chest auscultation for crackles. Submitted for publication to Chest 1985.

55. Murphy RLH, Gaensler EA, Holford SK, Del Bono EA, Epler GR. Crackles in the early detection of asbestosis. Am Rev Respir Dis 1984; 129: 375–79.

56. Murphy RLH. Holford SK, Knowler WC. Visual lung sound characterization by time-expanded wave-form analysis. N Engl J Med 1977; 296:968–71.

57. Murphy RLH, Gaensler EA, Ferris BG, Fitzgerald M, Sollidayl N, Morrisey W. Diagnosis of "Asbestosis." Observations from a longitudinal survey of shipyard pipe coverers. Am J Med 1978; 65:488–98.

58. Weill H, Ziskind MM, Waggenspack C, et al. Lung function consequences of dust exposure in asbestos cement manufacturing plants. Arch Environ Health 1975; 30:88.

59. Becklake MR, Fournier-Massey G, Rossiter C, et al. Lung function in chrysotile asbestos mine and mill workers of Quebec. Arch Environ Health 1972; 24:401.

60. Epler GR, McLoud TC, Gaensler EA, Mikus JP, Carington CB. Normal chest roentgenograms in chronic diffuse infiltrate lung disease. N Engl J Med 1978; 298:934–39.

61. Jodoin G, Gibbs W, Macklem PT, McDonald JC, Becklake M. Early effects of asbestos exposure on lung function. Am Rev Respir Dis 1971; 104:525.

62. Murphy RLH, Ferris BG, Burgess WA, et al. Effects of low concentrations of asbestos. Clinical, environmental, radiologic and epidemiologic observations in shipyard pipe coverers and controls. N Engl J Med 1971; 285:1271.

63. Langland JAM, Wallace W, Simpson M. Industrial workers in Belfast. 2. Morbidity in men still at work. Brit J Ind Med 1971; 28:217–72.

64. Murphy RLH, Soreuson K. Chest auscultation in the diagnosis of pulmonary asbestosis. J Occ Med 1973; 15:272.

65. Chiappino G, Zedda S. Value and significance of some diagnostic parameters in workers exposed to asbestos. Securitas Anno (Italy) 1973; 58:841. 27:163.

66. Reger RB, Young A, Morgan WKC. An accurate and rapid method of determining total lung capacity. Thorax 1972; 27:163.

67. Jodoin G, Gibbs GW, Macklem PT, et al. Early effects of asbestos exposure on lung function. Am Rev Respir Dis 1971; 104:525.

68. Konietzko N, Gerke E, Schlene H, et al. Closing volume in workers exposed to asbestos (German). Prax Pneumol 1974; 28:829.

69. Thomson ML, McGrath MW, Smither WJ, et al. Some abnormalities in measurement of pulmonary diffusion in asbestosis with chronic bronchitis and emphysema. Clin Sci 1961; 21:1.

70. Becklake MR. Asbestos exposure and airway disease. In: Gee JB, Morgan WK, Brooks SF, eds. Occupational lung disease. New York: Raven Press, 1984.

71. Selikoff IJ. The occurrence of pleural calcification among asbestos insulation workers. Biological effects of asbestos. Ann N Y Acad Sci 1965; 132:351–67.

72. Gilson JC. Asbestos Health Hazards: Recent observations in the United Kingdom. Proceedings of the International Conference on Pneumoconiosis, Johannesburg, South Africa, London: Oxford University Press, 1969.

likely to prove more effective in detecting the earliest changes in asbestosis. Intuitively, one test is likely to become abnormal first. It is likely that the first abnormality is not always the same one (e.g., one worker may have only an abnormal $D_L$ [69], and another only crackles as the first manifestation). This has been demonstrated with respect to restrictive lung function pattern and reduced $D_L$. It is likely that observations will have to be made in large groups over long periods to delineate clearly the best single test for early diagnosis of asbestosis if, indeed, a single initial abnormality exists.

### *Differential Diagnosis*

Streaky densities on chest films consistent with a parenchymal disease have many causes. All alternative diagnoses must be considered before accepting the presumptive diagnosis of asbestosis.

Occasionally, asbestosis is coexistent with chronic obstructive pulmonary disease. Evidence is accumulating that obstruction may also be related to an individual's occupational exposure (70). The relative importance of cigarette smoking and asbestos in the development of the combined problem of restrictive and obstructive disease may be difficult or even impossible to assess.

Since a not uncommon feature of asbestos exposure is bilateral pleural thickening, the question arises as to the helpfulness of such thickening in indicating that a patient with pulmonary fibrosis has asbestosis. Indeed, asbestos appears to be a rather potent stimulus for the development of pleural abnormalities. Selikoff found pleural fibrosis in 65% of persons he studied 40 years from the onset of their initial exposure to asbestos. With patients with no known exposure to asbestos or other known hazardous materials (71), the question arises as to whether an indirect or occult exposure to asbestos might have caused the pleural thickening. Severe diffuse pleural thickening is not common even in asbestos exposure. It was present in only 2.5% of the asbestos workers studied by Selikoff. Since there were no controls in that study, it is difficult to be certain that asbestos was the cause of the pleural fibrosis in those subjects. Indeed, Gilson reported in 1969 that pleural thickening was found on 187 of 3,860 (0.05%) routine roentgenograms of the chest in Great Britain (72). He conducted one of the few objective studies of pleural thickening by comparing the asbestos exposure of 113 of the 187 subjects with that of 113 age- and sex-matched controls. He found "a slight but unimpressive excess of positive histories of exposure to asbestos among the cases." Thus, it is not necessary to assume an occult exposure to asbestos in every instance of pleural thickening; the presence of pleural thickening is not definitive evidence of asbestos exposure. In another study, bilateral pleural thickening was found in 52 of 824 consecutive patients admitted to the hospital. Only 13 of these 52 had definite asbestos exposure as compared to 2 of 32 age-matched controls. In contrast to the relatively nonspecific finding of pleural thickening, the demonstration of pleural plaques with or without calcification is better evidence of asbestos exposure. Unfortunately, the latter usually occurs only many years after the onset of the exposure, thus limiting usefulness of early diagnosis.

A major problem exists in the differential diagnosis when more than one disease is present, whether it is congestive heart failure, COPD, or other chronic lung disease. There are diseases unrelated to asbestos exposure but with similar symptoms, and these may occur in some persons with asbestos exposure. However, given a clear history of exposure to asbestos, a diffuse interstitial fibrosis can be presumed to be due to the asbestos as other forms of interstitial fibrosis are relatively uncommon. The prevalence of lesser degrees of interstitial fibrosis is not well known and considerable caution has to be exercised in attributing all such phenomena to asbestos exposure, either known or occult.

## Summary

This document has focused on clinically detectable interstitial fibrosis due to asbestos exposure. While direct examination of lung tissue is the most reliable method of diagnosis, as stated above, this is rarely indicated in the assessment of workers for compensation purposes. Open lung biopsy is indicated in our opinion only when a clear health, rather than financial, benefit is likely to be provided. In the absence of pathologic examination of lung tissue, the diagnosis of asbestosis is a judgement based on a careful consideration of all relevant clinical findings. In our opinion, it is necessary that there be:

1. A reliable history of exposure.
2. An appropriate time interval between exposure and detection (see pages 9–10)

Furthermore, we regard the following clinical criteria to be of recognized value:

1. Chest roentgenographic evidence of type "s," "t," "u," small irregular opacifications of a profusion of 1/1 or greater
2. A restrictive pattern of lung impairment with a forced vital capacity below the lower limit of normal
3. A diffusing capacity below the lower limit of normal
4. Bilateral late or pan inspiratory crackles at the posterior lung bases not cleared by cough

Of these, the findings on the chest roentgenogram are the most important. When this criteria is not met, considerable caution is warranted. The specificity of the above criteria increases with increasing numbers of positive criteria. As in all clinical judgments, confounding variables, such as the presence of other clinical conditions that affect these criteria, should be evaluated.

It is possible that interstitial fibrosis may be present even though none of these criteria are satisfied, but, in our opinion, in these circumstances the clinical diagnosis cannot be made.

This statement was prepared by an Ad Hoc Committee of the Scientific Assembly on Environmental and Occupational Health in conjunction with the American College of Chest Physicians. The members of the Committee were:

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## References

1. Hamilton A, Hardy H. Industrial toxicology. Ed. 3, Publishing Sciences Group Inc., Acton, MA, 1974; 421.

2. Gilson GC. Asbestos cancer: Past and future hazards. Proc R Soc Med 1973; 66: 395.

3. Zussman J. Asbestos: Nature and history. Rev. Ciba Geigy 1972; 2: 3.

4. Smither WJ. Asbestos and asbestosis. Ann Occup Hyg 1970; 13: 3.

5. Biological effects of asbestos. Selikoff IJ, Churg J. Co-chairmen, Proceedings of a conference held at the New York Academy of Sciences, Oct. 19-21, 1964. Ann N Y Acad Sci, 1965; 132:1–766.

6. Biological effects of asbestos. Anspach M, Chairman Deutsches Zentralinstitut fur Arbeitsmedizin: Gesellschaft fur Arbeitshygiene and Arbeitsschutz in der DDR. Dresden (April 22-25) 1968; 1–312.

7. Biological effects of asbestos. Bogovski P; Gilson JG; Timbrell V, Wagner JC, eds. Proceedings of a working conference at IARC, Lyon, October 2-6, 1972, IARC Scientific Publications No. 8, Lyon 1973; 1–341.

8. Proceedings of the Pneumoconiosis Conference. Johannesburg, South Africa, February 1959, Orenstein AJ, ed, J and A Churchill Ltd., London 1960; 1–629.

9. Pneumoconiosis. Shapiro HA, ed, Proceedings of the International Conference, Johannesburg, South Africa, 1969, Oxford University Press, Cape Town, 1970; 3–645.

10. Parkes WR. Asbestos-related disorders. Brit J Dis Chest 1973; 67:261.

11. Stell PM, McGill T. Asbestos and laryngeal carcinoma. Lancet 1973; 2: 416.

12. Newhouse ML, Berry G. Asbestos and laryngeal carcinoma. Lancet, 1973, 2, 615.

13. Libshitz HI, Wershba MS, Atkinson GW, Southard ME. Asbestos and carcinoma of the larynx. JAMA 1974; 228: 1571.

14. Guidotti TL, Abraham JL, DeNee PB. Asbestos exposure and cancer of the larynx. West J Med 1975; 122: 75.

15. Graham J, Graham R. Ovarian cancer and asbestos. Environ Res 1967; 1: 115.

16. Doniach I, Swettenham KV, Hathorn MKS. Prevalence of asbestos bodies in a necropsy series in East London: Association with disease, occupation, and domiciliary address. Br J Ind Med 1975; 32: 16.

17. Weiss W. Clinical epidemiology. Arch Environ Health 1970; 20: 5.

18. Speil S, Leineweber JP. Asbestos minerals in